

**UNITED STATES AIR FORCE  
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**CRITICAL KNOWLEDGE GAPS CONCERNING  
PHARMACOLOGICAL FATIGUE  
COUNTERMEASURES FOR SUSTAINED AND  
CONTINUOUS AVIATION OPERATIONS**

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## SUMMARY

The purpose of this literature search was to identify knowledge gaps concerning the potential uses of pharmacological fatigue countermeasures in aviation. This type of review is a necessary step in developing an operationally based, safe-to-fly pharmacological doctrine that extends mission performance without introducing unwanted side effects. The review was conducted with respect to seven potential pharmacological countermeasures to fatigue: dextroamphetamine, modafinil, caffeine, temazepam, zolpidem, zaleplon, and melatonin. Thirty-four operationally relevant terms and phrases, such as acceleration, memory, computational performance, and predisposition to heat injury, were used. The searches were conducted in ten different on-line, scientific and medical databases on literature published in or after 1980. Of the hundreds of returned citations, 117 were relevant and are categorized, and the obvious knowledge gaps discussed. Aggressive research is indicated for both non-pharmacological and pharmacological countermeasures to fatigue.

### Recommendations

Combat and other flight stresses increase adrenergic output, helping the crewmember overcome the fatigue. However, this seems to produce a significant "letdown" after the combat interaction. This real-world performance letdown needs to be documented objectively in a manner that will lead to the development of effective fatigue countermeasures.

We need to develop new performance metrics in flight simulation and validate them with actual performance in the air. This will help us predict more accurately the level of aircrew fatigue and performance degradation in flight, and allow us to improve the effectiveness of fatigue countermeasures that limit risks to aircrews.

The known sympathomimetic properties of stimulants such as dextroamphetamine suggest that acceleration tolerance should be improved due to central and peripheral hypertensive effects. No relevant data were found to address this issue.

Future re-reviews of the literature such as this one would benefit from neuropsychiatry and pharmacology input to assess potential drug interactions with, for example, quinolones and doxycycline.

The residual presence of a drug and its metabolic products in blood and tissue may continue to cause cognitive problems after one or more half-lives. Empiric investigations of cognition are required to detect these problems. These investigations must be designed with high statistical power.

Aircrew may be awakened for unexpected operations before reaching even one half life of sleep aid metabolism. Investigations of benzodiazepine reversal with flumazenil will be helpful in terms of clarifying the nature of that reversal process.

We need to determine the optimal combinations (timing and dose) of sleep and alertness aids. The extent of neurotransmitter depletion and/or enhancement is not known for such combinations. Similarly, the polypharmacological effects on cognition are unknown.

All of our military fatigue laboratories should collaborate to acquire data that may be used to improve the power and comprehensiveness of pharmacological fatigue countermeasure research and, ultimately, provide the service member additional safety and efficacy in the field.

## PREFACE

Thank you to the staff of the Brooks Air Force Base Aeromedical Library for the hours of assistance in ordering and processing the technical articles used for this review.

James C. Miller, Ph.D., CPE, Warfighter Fatigue Countermeasures R&D Program, Air Force Research Laboratory (AFRL/HEPM-WFC) served as the project manager for this effort. The project was carried out primarily by Maj (Dr.) Lee G. Saltzgaber under the auspices of the Residency in Aerospace Medicine, US Air Force School of Aerospace Medicine during the period 1 July 00 – 30 Jun 01.

# CRITICAL KNOWLEDGE GAPS CONCERNING PHARMACOLOGICAL FATIGUE COUNTERMEASURES FOR SUSTAINED AND CONTINUOUS AVIATION OPERATIONS

## INTRODUCTION

The purpose of this literature search was to identify knowledge gaps concerning the potential uses of pharmacological fatigue countermeasures in aviation. This type of review is a necessary step in developing an operationally based, safe-to-fly pharmacological doctrine that extends mission performance without introducing unwanted side effects.

Of those items that make up one's physiological state and therefore determine human performance, fatigue degrades mental sooner than physical performance (Evans, 1991; Krueger, 1991). The significant impact fatigue has made upon flying safety can be demonstrated by the 20-25% of aircraft accidents that have listed fatigue as a contributing factor (Lyman 1980; Hoey 1992). Numerous investigations document fatigue's role in reducing the effectiveness of one's judgment and decision-making process that can be transferred into operational strategy and tactics selection. Dawson (1997) found that just 18 hours of sustained wakefulness decreased mental performance by as much as 30%, and at 24 hours all subjects showed some cognitive and motor decrement. With partial sleep deprivation, alertness and performance decline more gradually. After several days of sleep debt, alertness and performance degrade to nearly the same levels seen following 1-2 days of total sleep deprivation, at which time the fully debilitating effects of sleep loss are taking place.

As sleep loss progresses, fatigue can threaten judgment and decision-making. Caldwell (1997) stated that "task-related details are missed and responses to task demands often do not occur and the aviator's ability to pay attention to flight instruments, radio communications, crew coordination, and navigational tasks is severely impaired by fatigue." The attribution of about 70% of aircraft accidents to human error (Feggetter, 1982) highlights the significant impact that fatigue can have upon all facets of flying. Fatigued pilots also make less frequent but larger control errors that appear earlier in the task while their poorest performances become progressively worse (Bartlett, 1942).

Several countries have used stimulants to reduce fatigue and increase performance since World War II. The United States Air Force has used stimulants irregularly since 1960 in a variety of conflicts (Vietnam War, 1986 Libyan Raid, and Operation Desert Storm). Stimulant use was terminated after the Gulf War and reestablished in 1996 for use by a single pilot aircraft during deployment greater than 8 hours or on missions less than 8 hours when the departure was during their normal sleep cycle. Most often, stimulant use was for transoceanic flight where the demands upon the pilot were limited. However, F-15C pilots did note significant fatigue when flying combat air patrol missions over Iraq. More recently, stimulant availability has been extended by Air Combat Command to long-duration bomber missions.

Whether it provides general activation (amphetamine, caffeine) or stimulates only the waking systems (modafinil) as Jouvet (1997) proposed, the alertness aid of choice should support



wakefulness, vigilance and performance without interfering with sleep induction or recovery sleep when aircrew have the opportunity to sleep.

Desynchronization of circadian rhythms due to deployment across numerous meridians significantly impacts one's ability to sleep and adapt to a new time zone. Krueger (1991) noted that psychomotor vigilance performance (sustained cognition, vigilance, and response time) after a six-hour transmeridian flight drops 8-10% during the first day and demonstrates even more degradation in the early morning (0230-0600). When these circadian lows coincide with critical phases of flight (take off, landing, air-to-air refueling (AAR,) low altitude, intercepts, and ordinance delivery), the effectiveness of the pilot can be significantly affected. A 509<sup>th</sup> B-2 bomber pilot from Whiteman AFB, Mo expressed concern about his unit's inability to take "go" pills their 20-36 hour missions during the Operation Allied Force's After Action Medical Review in Mar 2000. The fatigue that developed over these missions placed them at increased risk because the multiple AAR's before and after the adrenaline surge associated with the enemy threats while performing their combat missions occurred over a variety of circadian peaks and troughs. The lack of stimulant use program for multiple seat aircraft was identified as a top priority due to the prolonged attention, vigilance, and performance increase the physiological requirements on aircrew and increases their risk for mission failure. In light of this, scheduling should be done so that local flights at the deployed location should be aligned with the adjusting body clock so that they might equate to a less demanding evening sortie instead of a night sortie when fatigue in conjunction with a circadian low might play a more significant factor in their performance.

Sustained<sup>1</sup> and continuous<sup>2</sup> operations demand that safe-to-fly evaluations of a medication include those unique parameters found in military aviation. Environmental stressors of heat, cold, noise, and vibration impact aircrew vigilance and can affect performance during prolonged periods of sustained attention. Evolving enemy threats require consistent improvements in avionics, ordinance, and human weapons systems. Concurrently, these improvements require increasing pilot vigilance when performing low altitude ground attack during instrument meteorological conditions at night. Any decrements in visual (especially night and vision aided with night vision goggles) or auditory perception can significantly limit assimilation of necessary information to coordinate with friendly forces or detect and persecute enemy forces, equipment, or structures. Any vestibular malfunction would increase the risk for a loss of spatial situational awareness several fold. Any clouding or altering of consciousness would impair cognitive performance. Interactions with nuclear-biological-chemical (NBC) medications associated with ground testing procedures, gender differences, synergy of the combination of medications, and reversibility need to be addressed. Decrements in manual dexterity, strength, aerobic capacity, or heat or acceleration tolerance might require limiting mission parameters. Reduced time of useful consciousness or increased risk of decompression at altitude significantly increase an aircrew's opportunities for idiosyncratic reactions. Acknowledging the increased demand and subsequent risk to mission and aircrew, the Air Force Medical Operations Agency (1999) evaluated its current operations and identified

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<sup>1</sup> SUSOPS: Shifts greater than 12 hr where one works nonstop for as long as possible.

<sup>2</sup> CONOPS: Uninterrupted schedule employing workers on regular schedules (7-12 hrs) that relieve the other workers,

fifteen Human Weapons System (HWS) Deficiencies and Priorities to protect the aircrew and optimize operational capabilities. Four of the top six (Sustained Operations, Performance Sustainment and Protective Gear, Night Operations, and Simulators and Distributive Mission Training) can be affected by the use of alertness aids and sleep aid medications.

## METHODS

This literature review was conducted to determine the gaps in knowledge on operationally relevant variables with respect to seven potential pharmacological countermeasures to fatigue:

### Alertness Aids

- Dextroamphetamine
- Modafinil
- Caffeine

### Sleep Aids

- Temazepam
- Zolpidem
- Zaleplon
- Melatonin

These seven medications were all searched against the following, operationally relevant terms and phrases (presented here in alphabetical order), occurring in the title, abstract, and descriptor or key word fields:

Acceleration	Hypoxia	Sleep interference
Altitude	NBC	Strength
Amnesia or memory	Night vision goggles	Subjective fatigue
Ciprofloxacin	Noise	Tracking
Cognition or judgment	Predisposition to cold injury	Vestibular effects
Computational performance	Predisposition to heat injury	Vibration
Decompression	Psychomotor function	Vigilance
Doxycycline	Pyridostigmine	Vision
Exercise capacity	Reaction time	
G Force	Reversibility	
Gender specificity	Sleep architecture	
Hearing	Sleep inertia	

Additionally, searches on the following terms and phrases were conducted to reveal pertinent topics and situations for and in which these medications were used:

- Sustained operations
- Continuous operations
- Performance enhancement and degradation
- Sleep enhancement and degradation
- Fatigue
- Military

The searches were conducted in the following databases:

Academic Search Elite

Military Library

Academic Search Premier	MEDLINE
Business Source Elite	Comp MEDLINE w/ MeSH
GRATEFULMED	PUBMED
MasterFILE Premier	PsycINFO

The year, 1980, was selected as the earliest search date to help limit the quantity of retrievals, with the understanding that it would preclude earlier, enlightening investigations of dextroamphetamine and caffeine. The review was limited to English language primary research papers, references from their bibliographies, and foreign language paper abstracts.

These search criteria and engines identified 462 articles from which 117 research and 38 background papers were selected. Evaluations of half-life, amnesic effects, and sedative-hypnotic properties have been well documented in pharmacodynamic literature and were excluded here. Investigations involving children less than 18, adults older than 60, or patients with mental or physical illness were excluded. Some investigations selected subjects based upon various criteria (e.g., quality of EEG) and were therefore excluded also because the general population of military pilots and aircrew are not selected in a similar manner.

Standard pharmacological evaluations of all medications address basic impacts upon human physiology, but are limited to experiences on the ground (ca. 1 gravity force, 747 mmHg air pressure, 21% oxygen,) and normal day wake-night sleep cycles. The operationally relevant investigations of alertness aids that were selected here investigated the alertness aid's effects upon 'fatigued' as opposed to 'rested' subjects, because the goal of a alertness aid is to restore and maintain vigilance, cognition, and performance. Alertness aid investigations were not selected if their goal was to enhance performance beyond baseline levels, because of the possibilities of long-term psychological and physical dependence. Hypnotic and sedative investigations were selected here if they addressed secondary effects or effects still present after awakening due to residual sedation. Most hypnotic-sedative investigations also included both diurnal and nocturnal administrations.

## **RESULTS**

The results of the literature search are presented in a series of tables, one table for each of the seven potential pharmacological countermeasures. Within each table, the studies are sorted into three categories: descriptive statistical assessments, inferential statistical assessments with sample size less than 30 and inferential statistical assessments with sample size greater than 30. Within each category, the number of citations listed in each cell indicates how many times a primary research article concluded that there was a "pro" (contributing to mission success) or "con" (detracting from mission success) effect. Each investigation usually had more than one finding so the total number of findings exceeds the number of articles. The relevant articles are listed by citation number in each cell.

## Alertness Aids

### Dextroamphetamine

There were 21 relevant investigations returned for dextroamphetamine (Table 1). No citations were returned that fit the following search topics: circadian rhythm adaptation, visual perception, night vision goggles, auditory perception, psychomotor function,

TABLE 1. Results of literature search concerning dextroamphetamine for descriptive studies and inferential studies with sample sizes less than and greater than 30.

	Descriptive		Experimental < 30		Experimental > 30	
	Con	Pro	Con	Pro	Con	Pro
Vestibular effects			1	2		
			11			
			4	33,115		
Cognition / Judgment				3		4
				96,101,102		3,75,76,81
Vigilance				1		
				102		
Computational Performance						2
						3,75
Psychomotor function				5		
				21,22,23,26,27		
Sleep architecture / length			1		1	
					2	
			93		0	
Memory				1		
				101		
Interference with Sleep			1		1	1
					2	
			29		0	76
Reaction Time				1		1
				33		81
Subjective Fatigue		2		6		3
		45,9		21,22,23,26,38,		
		5		96		75,76,81
Totals	0	2	3	19	2	11

## Modafinil

There were 13 relevant investigations returned for modafinil (Table 2). No citations were returned that fit the following search topics: circadian rhythm adaptation, night vision goggles, auditory perception, exercise capacity, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat injury, reversibility, NBC, pyridostigmine, ciprofloxacin, or doxycycline.

TABLE 2. Results of literature search concerning modafinil.

	Descriptive		Experimental < 30		Experimental > 30	
	Con	Pro	Con	Pro	Con	Pro
Visual Perception				3		
				8,63,84		
Vestibular effects				1		
				84		
Cognition / Judgment				5		2
				4,8,24,61,63		3,81
Vigilance				3		
				61,84,103		
Computational Performance				4		1
				4,61,63,84		3
Psychomotor function				6		
				5,8,24,25,61,63		
Predisposition to Cold Injury				1		
				16		
Gender specificity			1			
			113			
Sleep architecture / length					1	
					20	
Memory				3		
				5,8,63		
Interference with Sleep				1		1
				93		20
Reaction Time				5		1
				4,5,8,24,84		81
Subjective Fatigue				4		1
				24,25,61,62		81
Totals	0	0	1	36	0	7

### Caffeine

There were 16 relevant investigations returned for caffeine (Table 3). No citations were returned that fit the following search topics: circadian rhythm adaptation, night vision goggles, auditory perception, vestibular effects, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat or cold injury, gender specificity, reversibility, NBC, pyridostigmine, ciprofloxacin, doxycycline, sleep architecture / length, memory.

TABLE 3. Results of literature search concerning caffeine.

	Descriptive Experimental < 30 Experimental > 30					
	Con	Pro	Con	Pro	Con	Pro
Visual Perception				1		1
				92		66
Cognition / Judgment				2		2
				15,41		66,73
Vigilance				2		3
				15,92		57,66,91
Computational Performance				1		
				15		
Exercise capacity				1		
				10		
Psychomotor function		1		2		3
		7		53,85		57,73,97
Interference with Sleep				1		2
				15		58,97
Reaction Time				1		3
				92		57,66,91
Subjective Fatigue		1		3		5
		7		14,53,85		57,73,79,91,97
Totals	0	2	0	14	0	19



## Sleep Aids

### Temazepam

There were 29 relevant investigations returned for temazepam (Table 4). No citations were returned that fit the following search topics: night vision goggles, auditory perception, vestibular effects, g force, acceleration, hypoxia, decompression, vibration, noise, predisposition to heat or cold injury, reversibility, NBC, pyridostigmine, doxycycline, or sleep inertia.

TABLE 4. Results of literature search concerning temazepam.

	Descriptive		Experimental < 31		Experimental > 31	
	Con	Pro	Con	Pro	Con	Pro
Circadian rhythm adaptation			1			
			41			
Visual Perception				5		
				31,42,48,50,67		
Cognition / Judgment				7		1
				42,51,64,87, 104,111,112		82
Vigilance				2		
				30,111		
Computational Performance				1		
				112		
Exercise capacity			1	1		
			59	31		
Psychomotor function			1	5		
			12	18,31,48,60,67		
Strength				1		
				48		
Altitude				2		
				44,90		
Gender specificity			1	1		
			40	99		
Ciprofloxacin				1		
				56		
Sleep architecture / length			1	1		
			88	46		
Amnesia / Memory				1		
				104		
Residual Effects	2	3	10		2	
				18,42,48,51,64,67, 83,88,109,112		17,82
	1,77	11,30,50				

Reaction Time	3	4				
	<i>50,109,111</i>		<i>31,42,48,51</i>			
Subjective Fatigue		1			1	
		<i>30,44</i>			<i>17</i>	
Totals	0	2	11	43	0	4

## Zolpidem

There were 33 relevant investigations returned for temazepam (Table 5). No citations were returned that fit the following search topics: night vision goggles, auditory perception, vestibular effects, strength, g force, acceleration, altitude, decompression, vibration, noise, predisposition to heat injury, predisposition to cold injury, NBC, pyridostigmine, ciprofloxacin, or doxycycline.

TABLE 5. Results of literature search concerning zolpidem.

	Descriptive		Experimental < 30		Experimental > 30	
	Con	Pro	Con	Pro	Con	Pro
Circadian rhythm adaptation			1			
			35			
Visual Perception				1	1	
				86	36	
Cognition / Judgment			1	3		1
			106	8,28,47		2
Vigilance				1		
				39		
Computational Performance						1
						2
Exercise capacity				2		
				71,72		
Psychomotor function				5		
				8,32,39,47,98		
Hypoxia			1			
			69			
Gender specificity				2		
				49,94		
Reversibility		1	2	1		1
		65	68*,94*	78		110
Sleep architecture / length			1	5		
			35	6,28,47,72,74		
Sleep inertia				1		
				28		
Amnesia / Memory			5	4	2	
			39,43,54,89,106	9,32,47,70	36,52	
Residual Effects				11	1	
				9,13,19,28,39,47, 55,74,85,89,98	36	
Reaction Time				4	2	
				9,32,47,86	36,52	
Subjective Fatigue				1		
				28		

Totals	0	1	11	41	6	3
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### Zaleplon

There were 5 relevant investigations returned for temazepam (Table 6). No citations were returned that fit the following search topics: circadian rhythm adaptation, night vision goggles, auditory perception, cognition / judgment, vigilance, computational performance, exercise capacity, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat injury, predisposition to cold injury, gender specificity, reversibility, NBC, pyridostigmine, ciprofloxacin, doxycycline, sleep architecture / length, subjective fatigue.

TABLE 6. Results of literature search concerning zaleplon.

	Descriptive		Experimental < 30		Experimental > 30	
	Con	Pro	Con	Pro	Con	Pro
Visual Perception					1	
					36	
Vestibular effects				1		
				108		
Psychomotor function				2	2	
				106,108	36,52	
Sleep inertia				1		
				108		
Amnesia / Memory		2		1	2	
		106,108		43	36,52	
Residual Effects				1	1	
				108	36	
Reaction Time					1	
					36	
Totals	0	0	2	6	0	7

### Melatonin

There were 9 relevant investigations returned for temazepam (Table 7). No citations were returned that fit the following search topics: visual perception, night vision goggles, auditory perception, vestibular effects, exercise capacity, strength, g force, acceleration, hypoxia, altitude, decompression, vibration, noise, predisposition to heat injury, predisposition to cold injury, gender specificity, reversibility, NBC, pyridostigmine, ciprofloxacin, doxycycline, sleep inertia, or reaction time.

TABLE 7. Results of literature search concerning melatonin.

	Descriptive		Experimental < 30		Experimental > 30	
	Con	Pro	Con	Pro	Con	Pro
Circadian rhythm adaptation		2		2	1	
		37,107		34,80	100	
Cognition / Judgment		1		2		
		116		37,104		
Vigilance				1		
				34		
Computational Performance				1		
				117		
Psychomotor function				1		
				37		
Sleep architecture / length				1		
				117		
Amnesia / Memory				1		
				104		
Residual Effects				1		
				117		
Subjective Fatigue		1		1	1	
		116		80	105	
Totals	0	0	4	11	1	1

## DISCUSSION

Due to the reduced size of our military forces, post-cold war global power projection has required that fewer people work more hours to maintain peace and stability. This has also necessitated a concurrent increase in trans-meridian deployments and the need for immediate operational capability upon employment. In turn, our personnel have been exposed to a greater likelihood of suffering from circadian rhythm disturbance, sleep loss, and fatigue. The terrorist attacks of 11 September 2001 and the subsequent military mobilization have made things much worse<sup>3</sup>. All weather, continuous day and night operations, long duration flights enabled by inflight refueling, low-level flying, and dependence upon advanced technology also act to introduce significant fatigue and sleep deficit.

The resulting fatigue decreases an individual's accuracy and timing, increases the likelihood that he or she will accept poor performance as being adequate, decreases the ability to integrate information, and increases the likelihood of channelized attention with a resultant loss of situational awareness (Caldwell, 1997). Subsequent, fatigue-induced mission failures, loss of valuable aerospace platforms, and fatal mishaps may significantly impair force strength. Thus, aggressive research is indicated for both non-pharmacological and pharmacological countermeasures to fatigue.

Thinking in terms of pharmacological countermeasures, we do not advocate a medicated force. First, Air Force personnel need to be physically and emotionally fit and optimally trained to deal with the stresses of today's contingency environment. Efforts should be made to maximize aircrew health and confidence in their training and skill. Second, non-pharmacological fatigue countermeasures should be employed. These include training and education, dedication by management and individual to practice sleep hygiene and chronohygiene, fatigue-relevant approaches to mission scheduling, and decision assistance for the identification and management of fatigue-induced, mission-specific operational risks. Finally, we may use pharmacological countermeasures to sustain performance or to return performance to non-fatigued states. We do not advocate using alertness aids to improve the performance of non-fatigued warfighters beyond baseline.

### Alertness Aids

Surprisingly, the dextroamphetamine review revealed no articles concerning strength, exercise capacity or acceleration tolerance, and few articles addressing dizziness, a known side effect of dextroamphetamine. This apparent research gap was probably caused by the relatively recent (1980) cut-off date for the search.

The general stresses of aviation plus weather conditions, maintenance and communication issues, and the threat of being killed by the enemy or a mishap increase the body's adrenergic output, helping the crewmember overcome the effects of fatigue sufficiently to carry out a nighttime or long-duration mission. However, the adrenaline surge associated with putting "bombs on target on time" in a real mission seems to produce a significant "letdown" after the combat interaction. This letdown may introduce more fatigue-related performance

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<sup>3</sup> The number of operational consults performed by the Warfighter Fatigue Countermeasures R&D staff for Air Force units involved in deployments and homeland defense increased from one or two per month to several times that number.

degradation than the degradation introduced in a simulator mission. The real-world performance letdown needs to be documented objectively in a manner that will lead to the development of effective fatigue countermeasures.

Caldwell (2000) assessed the sensitivity of simulators compared with inflight testing and found that the added stresses associated with actual flight decreased dextroamphetamine's effectiveness in aiding aviator performance. Thus, we need to develop new performance metrics in simulation and validate them with actual performance in the air. This will help us predict more accurately the level of aircrew fatigue and performance degradation in flight, and allow us to improve the effectiveness of fatigue countermeasures that limit risks to aircrews.

Although direct references to or experiments on the effects of alertness aids on acceleration tolerance were not found, the known sympathomimetic properties of stimulants such as dextroamphetamine suggest that acceleration tolerance should be improved due to central and peripheral hypertensive effects. Obviously, one would like to know about this issue when deciding between the use, for example, of dextroamphetamine or modafinil (when approved) as an alertness aid for long-duration fighter missions that may require acceleration tolerance.

#### Sleep Aids

The temazepam search revealed few several investigations that addressed effects on vestibular function. This was surprising because dizziness is a major side effect of temazepam. Many of the 'con' investigations evaluated cognitive functions within two half lives of ingestion, a period within which one would expected to detect dizziness, if present.

Zolpidem has vertigo as one of its major reported side effects but no investigations evaluated this potentially dangerous side effect. There are both diplopia and vision abnormalities described in the pharmacological literature as zolpidem side effects and only two investigations were found that evaluated this side effect.

Concerning zaleplon, only one investigation on vestibular affects was found despite the fact that this is listed as one of the major side affects. Attention also needs to be directed at its potential for memory disturbance record.

Investigations of melatonin were more concerned with circadian resynchronization than its hypnotic capability. Thus, comparisons with the other sedative/hypnotics was difficult.

In general, sleep aids produce drowsiness and sedation, affect motor and mental performance, and may cause amnesia. Sleep aids are used to facilitate sleep at non-optimal times and in non-optimal places. They should help induce sleep rapidly without interfering with normal sleep architecture, allow users to awaken easily and/or respond to emergencies, and have no hangover or residual effects that may interfere with operations.

To some degree, insight into these issues may be gained by checking the half-life of a sleep aid. Few sleep-aid investigations of post-sleep performance have attempted to identify the



time needed to sufficiently clear the medication to define the minimal period between ingestion and mission planning. For temazepam, zolpidem, and zaleplon, differences in half-lives would predict fewer negative side or after effects with the latter two.

However, the residual presence of the drug and of its metabolic products in blood and tissue may continue to cause cognitive problems after one or more half-lives. Empiric investigations of cognition are required to detect these problems. These investigations must be designed with high statistical power, since type II statistical errors are of great concern here: that is, the investigation fails to detect cognitive impairment that actually exists. We base our acceptance of operational sleep aids, in part, on the basis of minimal post-sleep negative effects on cognition. Thus, we place ourselves in the position of trying to prove the negative. This is a specific weakness of the scientific method. This weakness may only be overcome through the use of designs of high statistical power and the replication of studies.

Aircrew may be awakened for unexpected operations before reaching even one half life of sleep aid metabolism. Meyler (2000) described mixed results for investigations of the reversal of sleep aid affects by Dexedrine. Investigations of benzodiazepine reversal with flumazenil will be helpful in terms of clarifying the nature of that reversal process.

#### Polypharmacy and drug interactions

We need to determine the optimal combinations (timing and dose) of sleep and alertness aids. The extent of neurotransmitter depletion and/or enhancement is not known for such combinations. Similarly, the polypharmacological effects on cognition are unknown. Future re-reviews of the literature such as this one would benefit from neuropsychiatry and pharmacology input to help assess potential drug interactions. As an example, quinolones significantly decrease caffeine's clearance rate. Thus, anthrax prophylaxis may affect expected improvements of alertness due to caffeine intake. Similarly, we need to examine the interactive effects of doxycycline on aircrew performance while taking alertness and sleep aids, since almost all aircrew will be taking it for malaria prophylaxis in indicated geographic areas.

All of our military fatigue laboratories should collaborate to acquire data that may be used to improve the power and comprehensiveness of pharmacological fatigue countermeasure research and, ultimately, provide the service member additional safety and efficacy in the field.

REFERENCES  
Numbered Reports Cited in Tables

1. Baird JA, Coles PK, Nicholson AN (1983). "Human Factors and Air Operations in the South Atlantic Campaign: Discussion Paper." Journal of the Royal Society of Medicine 76(11): 933-7.
2. Balkin TJ, O'Donnell VM, Wesensten N, McCann U, Belenky G (1992). "Comparison of the Daytime Sleep and Performance Effects of Zolpidem Versus Triazolam." Psychopharmacology 107(1): 83-8.
3. Baranski JV, Pigeau RA (1997). "Self-Monitoring Cognitive Performance During Sleep Deprivation: Effects of Modafinil, D-Amphetamine and Placebo." Journal of Sleep Research 6(2): 84-91.
4. Baranski JV, Cian C, Esquivie D, Pigeau RA, Raphel C (1998). "Modafinil During 64 hr of Sleep Deprivation: Dose-Related Effects on Fatigue, Alertness, and Cognitive Performance." Military Psychology 10(3): 173-93.
5. Batejat DM, Lagarde DP (1999). "Naps and Modafinil as Countermeasures for the Effects of Sleep Deprivation on Cognitive Performance." Aviation, Space, and Environmental Medicine 70(5): 493-8.
6. Beaumont M, Goldenberg F, Lejeune D, Marotte H, Harf A, Lofaso F (1996). "Effect of Zolpidem on Sleep and Ventilatory Patterns at Simulated Altitude of 4,000 Meters." American Journal of Respiratory and Critical Care Medicine 153(6 Pt 1): 1864-9.
7. Belland KM, Bissell C (1994). "A Subjective Investigation of Fatigue During Navy Flight Operations over Southern Iraq: Operation Southern Watch." Aviation, Space, and Environmental Medicine 65(6): 557-561.
8. Bensimon G, Foret J, Warot D, Lacomblez L, Thiercelin JF, Simon P (1990). "Daytime Wakefulness Following a Bedtime Oral Dose of Zolpidem 20 mg, Flunitrazepam 2 mg and Placebo." British Journal of Clinical Pharmacology 30(3): 463-9.
9. Bensimon G (1991). "Antagonism by Modafinil of the Psychomotor and Cognitive Impairment Induced by Sleep-Deprivation in 12 Healthy Volunteers." European Psychiatry 6: 93-7.
10. Berglund B, Hemmingsson P (1982). "Effects of Caffeine Ingestion on Exercise Performance at Low And High Altitudes in Cross-Country Skiers." International Journal of Sports Medicine 3(4): 234-6.
11. Betts TA, Birtle J (1982). "Effect of Two Hypnotic Drugs on Actual Driving Performance Next Morning." British Medical Journal (Clinical Research Edition) 285(6345): 852.

12. Bittencourt PR, Wade P, Smith AT, Richens A (1983). "Benzodiazepines Impair Smooth Pursuit Eye Movements." British Journal of Clinical Pharmacology 15(2): 259-62.
13. Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P (1999). "Residual Effect of Zolpidem 10 mg and Zopiclone 7.5 mg versus Flunitrazepam 1 mg and Placebo on Driving Performance and Ocular Saccades." Psychopharmacology (Berlin) 143(4): 373-9.
14. Bonnet MH, Gomez S, Wirth O, Arand DL (1995). "The Use of Caffeine versus Prophylactic Naps in Sustained Performance." Sleep 18(2): 97-104.
15. Borland RG, et. al. (1986). "Performance Overnight in Shiftworkers Operating a Day-Night Schedule." Aviation, Space, and Environmental Medicine 57(3): 241-249.
16. Bourdon L, Jacobs I, Bateman WA, Vallerand AL (1994). "Effect of Modafinil on Heat Production and Regulation of Body Temperatures in Cold-Exposed Humans." Aviation, Space, and Environmental Medicine 65(11): 999-1004.
17. Bricknell MC (1991). "Sleep Manipulation Prior to Airborne Exercises." Journal of the Royal Army Medical Corps 137(1): 22-6.
18. Briggs RS, Castleden CM, Kraft CA (1980). "Improved Hypnotic Treatment Using Chlormethiazole and Temazepam." British Medical Journal 280(6214): 601-4.
19. Brunner DP, Dijk DJ, Munch M, Borbely AA (1991). "Effect of Zolpidem on Sleep and Sleep EEG Spectra in Healthy Young Men." Psychopharmacology 104(1): 1-5.
20. Buguet A, Montmayeur A, Pigeau R, Naitoh P (1995). "Modafinil, D-Amphetamine and Placebo during 64 Hours of Sustained Mental Work. II. Effects on Two Nights of Recovery Sleep." Journal of Sleep Research 4(4): 229-241.
21. Caldwell JA, Caldwell JL, Crowley JS, Jones HD (1995). "Sustaining Helicopter Pilot Performance with Dexedrine during Periods of Sleep Deprivation." Aviation, Space, and Environmental Medicine 66(10): 930-7.
22. Caldwell JA, Caldwell JL (1997). "An In-Flight Investigation of the Efficacy of Dextroamphetamine for Sustaining Helicopter Pilot Performance." Aviation, Space, and Environmental Medicine 68(12): 1073-80.
23. Caldwell JA, Caldwell JL, Crowley JS (1997). "Sustaining Female Helicopter Pilot Performance with Dexedrine During Sleep Deprivation." International Journal of Aviation Psychology 7(1): 15-36.
24. Caldwell JA, Smythe NK, Caldwell JL, Hall KK, Norman DN (1999) "The Effects of Modafinil on Aviator Performance During 40 Hours of Continuous Wakefulness: A UH-60

Helicopter Simulator Investigation." US Army Aeromedical Research Laboratory, Fort Rucker, AL.

25. Caldwell JA, Caldwell JL, Smythe NK, Hall KK (2000). "A Double-Blind, Placebo-Controlled Investigation of the Efficacy of Modafinil for Sustaining the Alertness and Performance of Aviators: A Helicopter Simulator Investigation." Psychopharmacology (Berlin, Germany) **150**(3): 272-82.

26. Caldwell JA, Smythe NK, Leduc PA, Caldwell JL (2000). "Efficacy of Dexedrine for Maintaining Aviator Performance during 64 Hours of Sustained Wakefulness: A Simulator Investigation." Aviation, Space, and Environmental Medicine **71**(1): 7-18.

27. Caldwell JA, Roberts KA (2000). "Differential Sensitivity of Using Simulators versus Actual Aircraft to Evaluate the Effects of a Stimulant Medication on Aviator Performance." Military Psychology **12**(4): 277-91.

28. Caldwell JA, Caldwell JL (1998). "Comparison of the Effects of Zolpidem-Induced Prophylactic Naps to Placebo Naps and Forced Rest Periods in Prolonged Work Schedules." Sleep **21**(1): 79-90.

29. Caldwell JL, Caldwell JA (1997). "Recovery Sleep and Performance Following Sleep Deprivation with Dextroamphetamine." Journal of Sleep Research **6**(2): 92-101.

30. Casagrande M, Ferrara M, Curcio G, Porcu S (1999). "Assessing Nighttime Vigilance through a Three-Letter Cancellation Task (3-LCT): Effects of Daytime Sleep with Temazepam or Placebo." Physiology and Behavior **68**(1-2): 251-6.

31. Charles RB, Kirkham AJ, Guyatt AR, Parker SP (1987). "Psychomotor, Pulmonary and Exercise Responses to Sleep Medication." British Journal of Clinical Pharmacology **24**(2): 191-7.

32. Cluydts R, De Roeck J, Cosyns P, Lacante P (1995). "Antagonizing the effects of experimentally induced sleep disturbance in healthy volunteers by lormetazepam and zolpidem." Journal of Clinical Psychopharmacology **15**(2): 132-7.

33. Collins WE (1988). "Some Effects of Sleep Loss on Vestibular Responses." Aviation, Space, and Environmental Medicine **59**(6): 523-9.

34. Comperatore CA, Lieberman HR, Kirby AW, Adams B, Crowley JS (1996). "Melatonin Efficacy in Aviation Missions Requiring Rapid Deployment and Night Operations." Aviation, Space, and Environmental Medicine **67**(6): 520-4.

35. Copinschi G, Akseki E, Moreno-Reyes R, Leproult R, L'Hermite-Baleriaux M, Caufriez A, Vertongen F, Van Cauter E (1995). "Effects of Bedtime Administration of Zolpidem on Circadian and Sleep-Related Hormonal Profiles in Normal Women." Sleep **18**(6): 417-24.

36. Danjou P, Paty I, Fruncillo R, Worthington P, Unruh M, Cevallos W, Martin P (1999). "A Comparison of the Residual Effects of Zaleplon and Zolpidem Following Administration 5 to 2 h Before Awakening." British Journal of Clinical Pharmacology **48**(3): 367-74.
37. Dawson D, Encel N, Lushington K (1995). "Improving Adaptation to Simulated Night Shift: Timed Exposure to Bright Light versus Daytime Melatonin Administration." Sleep **18**(1): 11-21.
38. DeJohn CA, Shappell SA, Neri DF (1992). "Effects of Dextromethamphetamine on Subjective Fatigue." Naval Aerospace Medical Research Lab, Pensacola FL.
39. Dingemans J, Bury M, Bock J, Joubert P (1995). "Comparative Pharmacodynamics of Ro 41-3696, a New Hypnotic, and Zolpidem after Night-Time Administration to Healthy Subjects." Psychopharmacology (Berlin, Germany) **122**(2): 169-74.
40. Divoll M, Greenblatt DJ, Harmatz JS, Shader RI (1981). "Effect of Age and Gender on Disposition of Temazepam." Journal of Pharmaceutical Science and Technology **70**(10): 1104-7.
41. Doireau P, B. D., Chauffard F, Enslen M, Tachon P, Pradella S, Lagarde D (1997). "Cognitive Performance during a 64-Hours Sleep Deprivation: Interest of a Slow Release Caffeine." Presented at Aeromedical Support Issues in Contingency Operations, Rotterdam, Netherlands.
42. Donaldson E, Kennaway DJ (1991). "Effects of Temazepam on Sleep, Performance, and Rhythmic 6- Sulphatoxymelatonin and Cortisol Excretion after Transmeridian Travel." Aviation, Space, and Environmental Medicine **62**(7): 654-60.
43. Drover D, Lemmens H, Naidu S, Cevallos W, Darwish M, Stanski D (2000). "Pharmacokinetics, Pharmacodynamics, and Relative Pharmacokinetic/Pharmacodynamic Profiles of Zaleplon and Zolpidem." Clinical Therapeutics **22**(12): 1443-61.
44. Dubowitz G (1998). "Effect of Temazepam on Oxygen Saturation and Sleep Quality at High Altitude: Randomized Placebo Controlled Crossover Trial." British Medical Journal **316**(7131): 587-9.
45. Emonson DL, Vanderbeek RD (1995). "The Use of Amphetamines in U.S. Air Force Tactical Operations During Desert Shield and Storm." Aviation, Space, and Environmental Medicine **66**(3): 260-3.
46. Ferrillo F, Balestra V, Carta F, Nuvoli G, Pintus C, Rosadini G (1984). "Comparison between the Central Effects of Camazepam and Temazepam. Computerized Analysis of Sleep Recordings." Neuropsychobiology **11**(1): 72-6.
47. Gieschke R, Cluydts R, Dingemans J, De Roeck J, De Cock W (1994). "Effects of Bretazenil vs. Zolpidem and Placebo on Experimentally Induced Sleep Disturbance in

Healthy Volunteers." Methods and Findings in Experimental and Clinical Pharmacology 16(9): 667-75.

48. Golby J, Hutson MA (1985). "Temazepam and the Perceptual-Motor Performance of Professional Footballers." British Journal of Sports Medicine 19(2): 115-8.

49. Greenblatt DJ, Harmatz JS, von Moltke LL, Wright CE, Durol AL, Harrel-Joseph LM, Shader RI (2000). "Comparative Kinetics and Response to the Benzodiazepine Agonists Triazolam and Zolpidem: Evaluation of Sex-Dependent Differences." Journal of Pharmacology and Experimental Therapeutics 293(2): 435-43.

50. Griffiths AN, Tedeschi G, Richens A (1986). "The Effects of Repeated Doses of Temazepam and Nitrazepam on Several Measures of Human Performance." Acta psychiatrica Scandinavica. Supplementum 332: 119-26.

51. Harry TV, Latham AN (1980). "Hypnotic and Residual Effects of Temazepam in Volunteers." British Journal of Clinical Pharmacology 9(6): 618-20.

52. Hindmarch I (2001). "Residual Effects of Zaleplon and Zolpidem Following Middle of the Night Administration Five Hours to One Hour before Awakening." Human Psychopharmacology Clinical and Experimental 16: 159-67.

53. Horne JA, Reyner LA (1996). "Counteracting driver sleepiness: effects of napping, caffeine, and placebo." Psychophysiology 33(3): 306-9.

54. Isawa S, Suzuki M, Uchiumi M, Murasaki M (2000). "The Effect of Zolpidem and Zopiclone on Memory." Nihon Shinkei Seishin Yakurigaku Zasshi 20(2): 61-9.

55. Jackson JL, Louwerens JW, Cnossen F, de Jong HT (1992). "Testing the Effects of the Imidazopyridine Zolpidem on Memory: An Ecologically Valid Approach." Human Psychopharmacology Clinical & Experimental 7(5): 325-330.

56. Kamali F, Herd B, Edwards C, Nicholson E, Wynne H (1994). "The Influence of Ciprofloxacin on the Pharmacokinetics and Pharmacodynamics of a Single Dose of Temazepam in the Young and Elderly." Journal of Clinical Pharmacology and Therapeutics 19(2): 105-9.

57. Kelly T (1993). "Repeated Administration of Caffeine During Sleep Deprivation Does Not Affect Cognitive Performance." Sleep Research 22: 336.

58. Kelly TL, Gomez S, Ryman D, McGeoy S, Rubin R (1998). "Effects of Repeated Doses of Caffeine during 64 Hours of Sleep Deprivation on Subsequent Recovery Sleep." Naval Health Research Center, San Diego, CA.

59. Keul J, Rokitzki L, Jakob E, Stockhausen W (1988). "[The Effect of Temazepam on the Functional Capacity and Metabolic and Cardiocirculatory Parameters in Consideration of the "Jet Lag" Syndrome]." Arzneimittelforschung 38(7): 919-22.
60. Kroboth PD, Smith RB, Stoehr GP, Juhl RP (1985). "Pharmacodynamic Evaluation of the Benzodiazepine-Oral Contraceptive Interaction." Clinical Pharmacology and Therapeutics 38(5): 525-32.
61. Lagarde D, Batejat D (1995). "Disrupted Sleep - Wake Rhythm and Performance: Advantages of Modafinil." Military Psychology 7(3): 165-91.
62. Lagarde D, Batejat D, Van Beers P, Sarafian D, Pradella S (1995). "Interest of Modafinil, a New Psychostimulant, During a Sixty-Hour Sleep Deprivation Experiment." Fundamentals of Clinical Pharmacology 9(3): 271-9.
63. Lagarde D, Batejat D, Sicard B, Trocherie S, Chassard D, Enslen M, Chauffard F (2000). "Slow-Release Caffeine: a New Response to the Effects of a Limited Sleep Deprivation." Sleep 23(5): 651-61.
64. Lehmann W, Liljenberg B (1981). "Effect of Temazepam and Temazepam-Ethanol on Sleep." European Journal of Clinical Pharmacology 20(3): 201-5.
65. Lheureux P, Debailleul G, De Witte O, Askenasi R (1990). "Zolpidem Intoxication Mimicking Narcotic Overdose: Response to Flumazenil." Human and Experimental Toxicology 9(2): 105-7.
66. Lorist M (1994). "Influence of Caffeine on Selective Attention in Well-Rested and Fatigued Subjects." Psychophysiology 31: 525-34.
67. Mattila MJ, Aranko K, Mattila ME, Stromberg C (1984). "Objective and Subjective Assessment of Hangover during Subacute Administration of Temazepam and Nitrazepam to Healthy Subjects." European Journal of Clinical Pharmacology 26(3): 375-80.
68. Mattila MJ, Nurminen ML, Vainio P, Vanakoski J (1998). "Zolpidem 10 mg Given at Daytime is Not Antagonized by 300 mg Caffeine in Man." European Journal of Clinical Pharmacology 54(5): 421-5.
69. McCann CC, Quera-Salva MA, Boudet J, Frisk M, Barthouil P, Borderies P, Meyer P (1993). "Effect of Zolpidem During Sleep on Ventilation and Cardiovascular Variables in Normal Subjects." Fundamentals of Clinical Pharmacology 7(6): 305-10.
70. Mintzer MZ, Frey JM, Yingling JE, Griffiths RR (1997). "Triazolam and Zolpidem: A Comparison of Their Psychomotor, Cognitive, and Subjective Effects in Healthy Volunteers." Behavioural Pharmacology 8(6-7): 561-74.

71. Mougin F, Simon-Rigaud ML, Mougin C, Bourdin H, Jacquier MC, Henriet MT, Davenne D, Kantelip JP, Magnin P, Gaillard RC (1992). "Met-Enkephalin, Beta-Endorphin and Cortisol Responses to Sub-Maximal Exercise after Sleep Disturbances." European Journal of Applied Physiology and Occupational Physiology 64(4): 371-6.
72. Mougin F, Simon-Rigaud ML, Davenne D, Bourdin H, Guiland JC, Kantelip JP, Magnin P (1992). "[Tolerance to Exertion after Sleep Reduction and after Taking a Hypnotic: Zolpidem]." Archives Internationales de Physiologie de Biochimie et de Biophysique 100(3): 255-62.
73. Muehlbach MJ, Walsh JK (1995). "The Effects of Caffeine on Simulated Night-Shift Work and Subsequent Daytime Sleep." Sleep 18(1): 22-9.
74. Nakajima T, Sasaki T, Nakagome K, Takazawa S, Ikebuchi E, Ito Y, Miyazawa Y, Tanaka M, Kanno O (2000). "Comparison of the Effects of Zolpidem and Zopiclone on Nocturnal Sleep and Sleep Latency in the Morning: a Cross-Over Investigation in Healthy Young Volunteers." Life Sciences 67(1): 81-90.
75. Newhouse PA, Belenky G, Thomas M, Thorne D, Sing HC, Fertig J (1989). "The Effects of D-Amphetamine on Arousal, Cognition, and Mood after Prolonged Total Sleep Deprivation." Neuropsychopharmacology 2(2): 153-64.
76. Newhouse PA, Penetar DM, Fertig JB, Thorne DR (1992). "Stimulant Drug Effects on Performance and Behavior after Prolonged Sleep Deprivation: A Comparison of Amphetamine, Nicotine, and Deprenyl." Military Psychology 4(4): 207-233.
77. Nicholson AN (1984). "Long-Range Air Capability and the South Atlantic Campaign." Aviation, Space, and Environmental Medicine 55(4): 269-70.
78. Patat A, Naef MM, van Gessel E, Forster A, Dubruc C, Rosenzweig P (1994). "Flumazenil Antagonizes the Central Effects of Zolpidem, an Imidazopyridine Hypnotic." Clinical Pharmacology and Therapeutics 56(4): 430-6.
79. Penetar DM (1991). "Caffeine Reversal of Sleep Deprivation Effects." Sleep Research 74.
80. Petrie K, Conaglen JV, Thompson L, Chamberlain K (1989). "Effect of Melatonin on Jet Lag after Long Haul Flights." British Medical Journal 298(6675): 705-7.
81. Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, Thompson M, Mac KI (1995). "Modafinil, D-Amphetamine and Placebo during 64 Hours of Sustained Mental Work. I. Effects on Mood, Fatigue, Cognitive Performance and Body Temperature." Journal of Sleep Research 4(4): 212-228.



82. Pishkin V, Lovallo WR, Fishkin SM, Shurley JT (1980). "Residual Effects of Temazepam and other Hypnotic Compounds on Cognitive Function." Journal of Clinical Psychiatry 41(10): 358-63.
83. Porcu S, Bellatreccia A, Ferrara M, Casagrande M (1997). "Acutely Shifting the Sleep-Wake Cycle: Nighttime Sleepiness after Diurnal Administration of Temazepam or Placebo." Aviation, Space, and Environmental Medicine 68(8): 688-94.
84. Raphel C, Esquivie D, Stivalet P, Cian C (1997). "Modafinil Effects on Spatial Cognition during 60 Hours of Sleep Deprivation." Presented at Aeromedical Support Issues in Contingency Operations, Rotterdam, Netherlands.
85. Reyner LA, Horne JA (2000). "Early Morning Driver Sleepiness: Effectiveness of 200 mg Caffeine." Psychophysiology 37(2): 251-6.
86. Richens A, Mercer AJ, Jones DM, Griffiths A, Marshall RW (1993). "Effects of Zolpidem on Saccadic Eye Movements and Psychomotor Performance: A Double-Blind, Placebo Controlled Investigation in Healthy Volunteers." British Journal of Clinical Pharmacology 36(1): 61-5.
87. Roehrs T, McLenaghan A, Koshorek G, Zorick F, Roth T (1984). "Amnesic Effects of Lormetazepam." Psychopharmacology Supplement 1: 165-72.
88. Roehrs T, Kribbs N, Zorick F, Roth T (1986). "Hypnotic Residual Effects of Benzodiazepines with Repeated Administration." Sleep 9(2): 309-16.
89. Roehrs T, Merlotti L, Zorick F, Roth T (1994). "Sedative, Memory, and Performance Effects of Hypnotics." Psychopharmacology (Berlin, Germany) 116(2): 130-4.
90. Roggla G, Moser B, Roggla M (2000). "Effect of Temazepam on Ventilatory Response at Moderate Altitude." British Medical Journal 320(7226): 56.
91. Rosenthal L (1991). "Alerting Effects of Caffeine after Normal and Restricted Sleep." Neuropsychopharmacology 4(2): 103-8.
92. Ruijter J, De Ruiter MB, Snel J (2000). "The Effects of Caffeine on Visual Selective Attention to Color: An ERP Investigation." Psychophysiology 37(4): 427-39.
93. Saletu B, Frey R, Krupka M, Anderer P, Grunberger J, Barbanoj MJ (1989). "Differential Effects of a New Central Adrenergic Agonist--Modafinil--and D-Amphetamine on Sleep and Early Morning Behaviour in Young Healthy Volunteers." International Journal of Clinical Psychopharmacology Research 9(3): 183-95.
94. Salva P, Costa J (1995). "Clinical Pharmacokinetics and Pharmacodynamics of Zolpidem. Therapeutic Implications." Clinical Pharmacokinetics 29(3): 142-53.

95. Senechal PK (1988). "Flight Surgeon Support of Combat Operations at RAF Upper Heyford." Aviation, Space, and Environmental Medicine 59(8): 776-7.
96. Shappell SA, Neri DF, DeJohn CA (1992). "Simulated Sustained Flight Operations and Performance, Part 2: Effects of Dextromethamphetamine." Naval Aerospace Medical Research Lab, Pensacola FL.
97. Sicard B, Lagarde D, Batejat D, Chaufford F, Enslen M, Tachon P (1997). "Slow Release Caffeine: A Valid Pharmacological Countermeasure." Presented at Aeromedical Support Issues in Contingency Operations, Rotterdam, Netherlands.
98. Sicard BA, Trocherie S, Moreau J, Vieillefond H, Court LA (1993). "Evaluation of Zolpidem on Alertness and Psychomotor Abilities among Aviation Ground Personnel and Pilots." Aviation, Space, and Environmental Medicine 64(5): 371-5.
99. Smith RB, Divoll M, Gillespie WR, Greenblatt DJ (1983). "Effect of Subject Age and Gender on the Pharmacokinetics of Oral Triazolam and Temazepam." Journal of Clinical Psychopharmacology 3(3): 172-6.
100. Spitzer RL, Terman M, Williams JB, Terman JS, Malt UF, Singer F, Lewy AJ (1999). "Jet Lag: Clinical Features, Validation of a New Syndrome-Specific Scale, and Lack of Response to Melatonin in a Randomized, Double-Blind Trial." American Journal of Psychiatry 156(9): 1392-6.
101. Stanny RR, Mccardie AH, Neri DF (1993). "Effects of Methamphetamine and Fatigue on Long- and Short-Term Memory." Naval Aerospace Medical Research Lab, Pensacola FL.
102. Stanny RR, Mccardie AH, Neri DF (1993). "Effects of Methamphetamine on Vigilance and Tracking during Extended Wakefulness." Naval Aerospace Medical Research Lab, Pensacola FL.
103. Stivalet P (1998). "Effects of Modafinil on Attentional Processes during 60 Hours of Sleep Deprivation." Human Psychopharmacology Clinical & Experimental 13(7): 501-7.
104. Stone BM, Turner C, Mills SL, Nicholson AN (2000). "Hypnotic Activity of Melatonin." Sleep 23(5): 663-9.
105. Suhner A, Schlagenhauf P, Johnson R, Tschopp A, Steffen R (1998). "Comparative Investigation to Determine the Optimal Melatonin Dosage Form for the Alleviation of Jet Lag." Chronobiology International 15(6): 655-66.
106. Troy SM, Lucki I, Unruh MA, Cevallos WH, Leister CA, Martin PT, Furlan PM, Mangano R (2000). "Comparison of the Effects of Zaleplon, Zolpidem, and Triazolam on Memory, Learning, and Psychomotor Performance." Journal of Clinical Psychopharmacology 20(3): 328-37.

107. Van Cauter E, Moreno-Reyes R, Akseki E, L'Hermite-Balyeriaux M, Hirschfeld U, Leproult R, Copinschi G (1998). "Rapid Phase Advance of the 24-H Melatonin Profile in Response to Afternoon Dark Exposure." American Journal of Physiology 275(1 PT 1): E48-54.
108. Vermeeren A (1998). "Residual Effects of Evening and Middle of the Night Administration of Zaleplon 10 and 20 mg on Memory and Actual Driving Performance." Human Psychopharmacology Clinical and Experimental 13: S98-107.
109. Warburton DM, Wesnes K (1984). "A Comparison of Temazepam and Flurazepam in Terms of Sleep Quality and Residual Changes in Activation and Performance." Arzneimittelforschung 34(11): 1601-4.
110. Wesensten NJ, Balkin TJ, Davis HQ, Belenky GL (1995). "Reversal of Triazolam and Zolpidem-Induced Memory Impairment by Flumazenil." Psychopharmacology (Berlin, Germany) 121(2): 242-9.
111. Wesnes K, Warburton DM (1984). "A Comparison of Temazepam and Flurazepam in Terms of Sleep Quality and Residual Changes in Performance." Neuropsychobiology 11(4): 255-9.
112. Wesnes K, Warburton DM (1986). "Effects of Temazepam on Sleep Quality and Subsequent Mental Efficiency under Normal Sleeping Conditions and Following Delayed Sleep Onset." Neuropsychobiology 15(3-4): 187-91.
113. Wong YN, King SP, Simcoe D, Gorman S, Laughton W, McCormick GC, Grebow P (1999). "Open-Label, Single-Dose Pharmacokinetic Investigation of Modafinil Tablets: Influence of Age and Gender in Normal Subjects." Journal of Clinical Pharmacology 39(3): 281-8.
114. Wood CD, Manno JE, Manno BR, Odenheimer RC, Bairnsfather LE (1986). "The Effect of Antimotion Sickness Drugs on Habituation to Motion." Aviation, Space, and Environmental Medicine 57(6): 539-42.
115. Wood CD, Manno JE, Wood MJ, Manno BR, Redetzki HM (1987). "Mechanisms of Antimotion Sickness Drugs." Aviation, Space, and Environmental Medicine 58(9 Pt 2): A262-5.
116. Wright SW, Lawrence LM, Wrenn KD, Haynes ML, Welch LW, Schlack HM (1998). "Randomized Clinical Trial of Melatonin after Night-Shift Work: Efficacy and Neuropsychologic Effects." Annals of Emergency Medicine 32(3 Pt 1): 334-40.
117. Zhdanova IV, Wurtman RJ, Morabito C, Piotrovskaya VR, Lynch HJ (1996). "Effects of Low Oral Doses of Melatonin, Given 2-4 Hours before Habitual Bedtime, on Sleep in Normal Young Humans." Sleep 19(5): 423-31.

#### Additional Resources

Advisory Group for Aerospace Research and Development, Neuilly-sur-France (1998). Aeromedical Support Issues in Contingency Operations.

Bartlett FC (1942). "Fatigue in the Air Pilot." FRPC Technical Report No. 488, University of Cambridge Psychological Laboratory, Cambridge, England.

Borowsky MS, Wall R (1983). "Naval Aviation Mishaps and Fatigue." Aviation, Space, and Environmental Medicine 54(6): 535-8.

Caldwell JA (1997). "Fatigue in the Aviation Environment: An Overview of the Causes and Effects as well as Recommended Countermeasures." Aviation, Space, and Environmental Medicine 68(10): 932-8.

Caldwell JA, Caldwell JL (2000). Investigating Pharmacological Performance Enhancement with Behavioral, Subjective, and Electroencephalographic Measures. in Engineering Psychophysiology: Issues and Applications, Lawrence Erlbaum Associates, Mahwah, NJ.

Caldwell JL (2000). "The Use of Melatonin: An Information Paper." Aviation, Space, and Environmental Medicine 71(3): 238-44.

Carlton PK (1999). Human Weapons System (HWS) Deficiencies and Priorities. Air Force Medical Operations Agency, Bolling AFB, DC.

Cornum R, Caldwell J, Cornum K (1997). "Stimulant Use in Extended Flight Operations." Airpower Journal Spring: 53-8.

Dawson D, Reid K (1997). "Fatigue, alcohol and performance impairment." Nature 388(6639): 235.

DeJohn CA, Reams GG (1992). An Analysis of a Sustained Flight Operation Training Mission in Navy Attack Aircraft, Naval Aerospace Medical Research Lab, Pensacola FL.

DeRenzo EG, Szafranski R (1997). "Fooling Mother Nature." Airpower Journal Summer(25-36).

Dinges DF (1995). "An Overview of Sleepiness and Accidents." Journal of Sleep Research 4(S2): 4-14.

Dukes MNG, Aronson JK (2000). Meyler's Side Effects of Drugs.

Evans SM, Mackie RR, Wylie DC (1991). Fatigue Effects on Human Performance in Combat: A Literature Review. Volume 1. Vector Research Inc., Ann Arbor MI.

- Feggetter AJ (1982). "A Method for Investigating Human Factor Aspects of Aircraft Accidents and Incidents." Ergonomics 25(11): 1065-75.
- Fraschini F, Stankov B (1993). "Temazepam: Pharmacological Profile of a Benzodiazepine and New Trends in Its Clinical Application." Pharmacological Research 27(2): 97-113.
- French J, Bisson RU, Neville KJ, Mitcha J, Storm WF (1994). "Crew Fatigue during Simulated, Long Duration B-1B Bomber Missions." Aviation, Space, and Environmental Medicine 65(5 Suppl): A1-6.
- Gander PH, Rosekind MR, Gregory KB (1998). "Flight Crew Fatigue VI: A Synthesis." Aviation, Space, and Environmental Medicine 69(9 Suppl): B49-60.
- Giam GC (1997). "Effects of Sleep Deprivation with Reference to Military Operations." Annals of the Academy of Medicine, Singapore 26(1): 88-93.
- Hitchcock L (1999). "Pilot Performance" in Garland DJ, Wise JA, Hopkin VD Handbook of Aviation Human Factors. Lawrence Erlbaum Associates, Mahwah, N.J.
- Hoey D (1992). "Fatigue Management." The Combat Edge September: 18-21.
- Horne J, Reyner L (1999). "Vehicle Accidents Related to Sleep: A Review." Occupational and Environmental Medicine 56(5): 289-94.
- Jones FD (1995). "US Air Force Combat Psychiatry" in Jones FD, Sparacino LR, Wilcox VL, Rothberg JM, Stokes JW War psychiatry. Office of the Surgeon General, United States Army, Falls Church, VA.
- Jouvet M (1997). Neurological Basis of the Pharmacological Management of Sustained Alertness. Presented at Aeromedical Support Issues in Contingency Operations, Rotterdam, Netherlands.
- Kelly TL (1996). Circadian Rhythms: Importance for Models of Cognitive Performance. Naval Health Research Center, San Diego CA.
- Krueger GP (1990). Sustained Military Performance in Continuous Operations: Combatant Fatigue, Rest and Sleep Needs. Army Aeromedical Research Lab, Fort Rucker AL.
- Lamarine RJ (1994). "Selected Health and Behavioral Effects Related to the Use of Caffeine." Journal of Community Health 19(6): 449-66.
- Li G, Baker SP, Grabowski JG, Rebok GW (2001). "Factors Associated with Pilot Error in Aviation Crashes." Aviation, Space, and Environmental Medicine 72(1): 52-8.

Lyman EG, Orlady HW (1980). Fatigue and Associated Performance Decrements in Air Transport Operations. NASA Contract Report 166167. NASA Ames Research Center, Moffett Field, CA.

Miller JC (2000). Safe-to-Fly Issue. Air Force Research Laboratory, Brooks AFB, TX.

Naitoh P, Kelly TL, Englund C (1990). "Health Effects of Sleep Deprivation." Occupational Medicine 5(2): 209-37.

Neri DF, Gadolin RE (1990). Sustained/Continuous Operations. Naval Aerospace Medical Research Lab, Pensacola FL.

Neri DF, Shappell SA (1994). "The Effect of Combat on the Work/Rest Schedules and Fatigue of Naval Aviators during Operations Desert Shield and Desert Storm." Military Psychology 6(3): 141-62.

Neri DF, Shappell SA, DeJohn CA (1992). "Simulated Sustained Flight Operations and Performance, Part 1: Effects of Fatigue." Military Psychology 4(3): 137-55.

Nicholson AN, Pascoe PA (1992). "Safe Use of Medication by Aircrew." Alcohol, Drugs and Driving 8(3-4): 225-9.

Price WJ, Holley DC (1990). "Shiftwork and Safety in Aviation." Occupational Medicine 5(2): 343-77.

Ramsey CS, McGlohn SE (1997). "Zolpidem as a Fatigue Countermeasure." Aviation, Space, and Environmental Medicine 68(10): 926-31.

Rosekind MR, Gander PH, Gregory KB, Smith RM, Miller DL, Oyung R, Webbon LL, Johnson JM (1997). "Managing Fatigue in Operational Settings 2: An Integrated Approach." Hospital Topics 75(3): 31-5.

Rosekind MR, Gander PH, Miller DL, Gregory KB, Smith RM, Weldon KJ, Co EL, McNally KL, Lebacqz JV (1994). "Fatigue in Operational Settings: Examples from the Aviation Environment." Human Factors 36(2): 327-38.

Stockey IH (2000). Drug Interactions: A Source Book of Adverse Interactions, their Mechanisms, Clinical Importance and Management. Blackwell Scientific Publications, Nottingham, England.

Stone BM, Turner C (1997). "Promoting Sleep in Shiftworkers and Intercontinental Travelers." Chronobiology International 14(2): 133-43.

Wright N (2001). "Vigilance on the Civil Flight Deck: Incidence of Sleepiness and Sleep during Long-Haul Flights and Associated Changes in Physiological Parameters." Ergonomics 44(1): 82-106.